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ASSESSMENT OF CENTRAL AUDITORY PROCESSING DISORDER IN CHILDREN AND ADOLESCENTS TREATED WITH METHYLPHENIDATE DUE TO ATTENTION DEFICIT DISORDER: SYSTEMATIC REVIEW

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Contributions:
A Study design/planning
B Data collection/entry
C Data analysis/statistics
D Data interpretation
E Preparation of manuscript
F Literature analysis/search
G Funds collection

Abstract

Background: Improvement in central auditory processing (CAP) test results has been reported in children with attention deficit disorder (ADD) who have been treated with methylphenidate (MPH).

Objective: To determine the effect of MPH on CAP tests in school-aged children and adolescents with ADD, with or without hyperactivity.

Methods: A systematic review was carried out following the Prisma methodology in The Cochrane Library, Medline, Embase, and Lilacs data bases. Randomized (RCT) and non-randomized (NRCT) clinical trials were included, involving male and female patients between 6 and 18 years old, with normal audition and intelligence and diagnosed with ADD; they were given MPH treatment and the results of CAP tests were compared to placebo or non-MPH treatment.

Results: Five studies (two RCTs and three NRCTs) reported on 187 participants of both sexes, between 6 and 15 years old, of which 135 individuals met the diagnostic criteria for ADD and 44 presented ADD with central auditory processing (CAP) disorder, with 52 individuals used as controls. MPH treatment produced an increase in the performance of the speech-in-noise test (0.38 SMD [95% CI 0.11 to 0.66] [Z = 2.7, $p = 0.007$]), staggered spondaic words test (0.35 SMD [95% CI 0 to 0.69] [Z = 1.95, $p = 0.05$]) and filtered word test, frequency pattern test, and phonemic synthesis test (0.35 SMD [95% CI 0.01 to 0.68] [Z = 2.03, $p = 0.04$]. Also, continuous performance tests showed a decrease in the number of errors and inattentions (–0.77 SMD [95% CI –1.17 to –0.37] [Z = 3.79, $p = 0.0002$]) concerning the control group. The evidence was consistent, accurate, and with low heterogeneity.

Conclusions: MPH has a significant and favorable effect on the CAP tests of children and adolescents with ADD.

Key words: Methylphenidate • attention deficit hyperactivity disorder • central auditory processing

OCENA ZABURZEŃ CENTRALNEGO PRZETWARZANIA SŁUCHOWEGO U DZIECI I MŁODZIEŻY LECZONYCH METYLOFENIDATEM Z POWODU ZABURZEŃ KONCENTRACJI: PRZEGLĄD SYSTEMATYCZNY

Streszczenie

Wstęp: U dzieci z zespołem zaburzeń koncentracji (ADD), które były leczone metylofenidatem (MPH), odnotowano poprawę wyników testu centralnego przetwarzania słuchowego (CAP).

Cel: Określenie wpływu MPH na wyniki testów CAP u dzieci i młodzieży w wieku szkolnym z ADD, z nadpobudliwością lub bez.

Metody: Systematyczny przegląd został przeprowadzony zgodnie z metodologią Prisma w bazach danych The Cochrane Library, Medline, Embase i Lilacs. Badania kliniczne były randomizowane (RCT) i nierandomizowane (NRCT), z udziałem pacjentów płci męskiej i żeńskiej w wieku od 6 do 18 lat, z prawidłowym słuchem i inteligencją oraz ze zdiagnozowanym ADD; pacjenci byli leczeni za pomocą MPH, a wyniki testów CAP porównano z badanymi, u których zastosowano placebo lub inne leki niż MPH.

Wyniki: Pięcioma badaniami (dwa RCT i trzy NRCT) objęto 187 uczestników obu płci, w wieku od 6 do 15 lat, z których 135 osób spełniało kryteria diagnostyczne ADD, a 44 miało ADD z zaburzeniami centralnego przetwarzania słuchowego (CAP). Grupę kontrolą stanowiły 52 osoby. Leczenie MPH wpłynęło na lepsze wyniki testu rozumienia mowy w szumie (0,38 SMD [95% CI 0,11 do 0,66] [Z = 2,7,

p = 0,007]), testu Staggered Spondaic Words (0,35 SMD [95% CI 0 do 0,69] [Z = 1,95, p = 0,05]) oraz testu słów filtrowanych, testu wzorców częstotliwości i testu syntezy fonemicznej (0,35 SMD [95% CI 0,01 do 0,68] [Z = 2,03, p = 0,04]. Testy wydajnościowe wykazały zmniejszenie liczby błędów i braku uwagi (–0,77 SMD [95% CI –1,17 do –0,37] [Z = 3,79, p = 0,0002]) w grupie kontrolnej. Uzyskane wyniki były spójne, dokładne i z niską heterogenicznością.

Wnioski: MPH ma istotny i korzystny wpływ na wyniki testów CAP u dzieci i młodzieży z ADD.

Słowa kluczowe: Metylofenidat • zespół nadpobudliwości psychoruchowej z zaburzeniami koncentracji • centralne przetwarzanie słuchowe

Abbreviations:

ADD: attention deficit disorder
CAP: central auditory processing
CAPD: central auditory processing disorder
MPH: methylphenidate
SMD: standardized mean difference
RCT: randomized clinical trials
GRADE: Grading of Recommendations Assessment, Development, and Evaluation
CI: Confidence interval
MeSH: Medical Subject Headings
FWT: filtered word test
FPT: frequency pattern test.
SN: speech-in-noise test
CPT: continuous performance test
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PST: phonemic synthesis test
SSW: staggered spondaic words

Background

The American Speech-Language-Hearing Association (ASHA) defines Central Auditory Processing Disorder (CAPD) as deficits in the neural processing of auditory information in the central auditory nervous system, not due to higher order language or cognition. It is demonstrated by poor performance in one or more of skills such as the location and lateralization of sounds, recognition of the type of auditory signal, temporary aspects of audition (resolution, masking, integration, and distribution), audition of simultaneous signals, and the inability to hear degraded acoustic signals, even though the auditory thresholds are within normal limits. Although sometimes difficult, careful differential diagnosis is important to the process of treatment planning [1, 2]. Moreover, attention deficit disorder (ADD) is defined as a syndrome characterized by inattention, hyperactivity, and impulsivity [3]. The evolution of both disorders can cause significant cognitive, personal, social, and academic changes [4–7].

CAPD and ADD have overlapping clinical characteristics, despite being different diseases that require appropriate and individualized therapeutic diagnoses and interventions [8, 9]. However, patients with ADD show a higher frequency of CAPD compared to the general population, so that they might share a common etiology, as well as have a similar therapeutic approach [10–12].

Psychostimulant drugs, such as MPH, are the standard pharmacological treatment for ADD in children over the age of 6 years [13]. Similarly, there are RCTs that report improvement of CAP in children with ADD; however, the data are controversial and insufficient [10,11,14,15]. Defining a favorable effect on CAP tests, such as discrimination, memory, attention, or auditory sequencing, with the intervention of the MPH would increase the therapeutic possibilities for these patients, with the potential of improving their quality of life and decrease serious consequences of the absence of treatment. Therefore, the purpose of this systematic review was to analyze those trials that have quantified the effect of MPH on school-aged children and adolescent patients diagnosed with ADD, as well as reporting CAP test results.

Material and methods

The present study was carried out by searching digital data sources on four platforms – The Cochrane Library, Medline, Embase, and Lilacs – relating to original clinical trials indexed in Spanish, English, or Portuguese and published between January 1990 and January 2019. The following Panamerican Health Organization (PHO) descriptors in health science were used (in Spanish and English): "lenguaje/language", "desarrollo del lenguaje/speech development", "trastorno por déficit de atención con hiperactividad/attention deficit hyperactivity disorder", "TDAH/ADHD", "trastorno de procesamiento auditivo central/auditory processing disorder", and "metilfenidato/methylphenidate". Two of the authors searched independently (P-RMA and S-RJA); the last search was conducted on 29 September 2019. The study was approved by the Institutional Committee.

Selection

Eligibility (carried out by P-RMA and S-RJA) was based on the following selection criteria Participants: Studies involving individuals with IQ in the normal range (IQ >70), aged 6 to 18 years, of either sex, with normal bilateral auditory tests, and diagnostic of ADD in accordance with the Diagnostic and Statistical Manual of Mental Disorders (third to fifth edition), or according to the International Classification of Diseases ninth or tenth reviews (CIE-9 or CIE-10 codes) [16] or presence of abnormalities in CAP psychoacoustic tests or CAPD diagnosis [17].

Comparison: Administration of MPH v. without MPH or use of placebo Results: Studies were sought that included the following CAP tests: speech in noise (SN) test, staggered spondaic words (SSW) test, continuous performance test (CPT), filtered word test (FWT), phonemic synthesis test (PST), and frequency pattern test (FPT).

Speech in noise (SN) test

This test evaluates the ability to identify monosyllabic words presented at 40 dB, and at 5 dB above the noise level in each ear [15].

Staggered spondaic words (SSW) test

The SSW test involves pairs of disyllabic words with a staggered start presented at 50 dB in relation to the average

of pure tones (0.5, 1, and 2 kHz) in each ear. The last syllable of the first word and the first syllable of the second word are spondaic. Spondaic syllables are simultaneously presented to opposite ears (dichotic). The remaining two monosyllabic words are presented in isolation to opposite ears. The patient is asked to reproduce the group of words heard in each ear [10].

Continuous performance test (CPT)

The CPT consists of a hearing surveillance task in which a patient hears a list of words (presented at 50 dB relative to the average pure tones) and is asked to raise a thumb every time he hears the target word. The test includes 20 familiar, monosyllabic words for young people or children (e.g., see, col, gis, light, gas), which are randomly mixed with the target word to form a list of 96 words submitted six times, for a total of 576 words. If the thumb is raised for words other than the target, this is considered an impulsivity error. If the thumb is never raised to the target word, this is considered inattention. The total number of impulsive and inattention errors are compared separately to age-appropriate scores [10].

Filtered word test (FWT)

In this test, a sentence is presented to both ears simultaneously. The sentence in the untested ear is presented 15 dB higher than the tested ear, and the child is asked to repeat the sentence heard in the test ear [18].

Phonemic synthesis test (PST)

PST assesses auditory memory and decoding ability. The subject must recognize the individual sounds that are presented one by one, put them together, and respond with the combined monosyllabic word (for example, "dress" for da-res). The presentation is 50 dB relative to the average pure tones (0.5, 1, and 2 kHz) in each ear. Test standards are available by grade level [10].

Frequency pattern test (FPT)

The FPT consists of 30 sequences of random three-tone patterns presented in each ear, yielding six different combinations of two frequencies (880 and 1430 Hz). Stimuli occur at an intensity of 50 dB HL above the average of hearing frequency thresholds. Participants are asked to respond and verbally classify the stimulus sequence and are evaluated by the number of correct responses [15].

Extracting information

The following data were collected from each study, including demographic characteristics of the patients and controls, criteria for inclusion and exclusion from the study, population sample sizes, type of CAP assessment, and raw data on the measures of the results. This process was carried out by P-RMA.

Assessment of the quality of studies included

We use the GRADE approach to assess the quality of evidence behind the treatment effects presented in this review

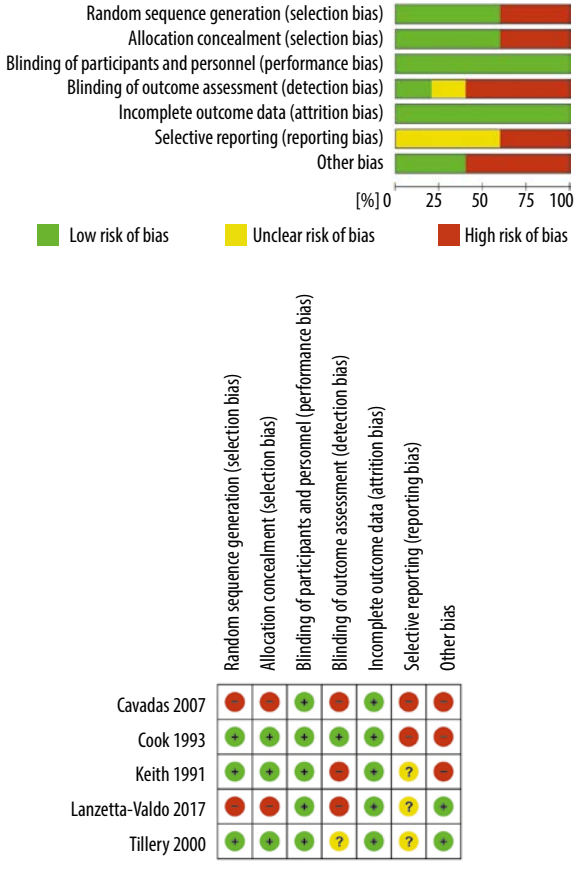


Figure 1. Summaries of the risk of bias. Two authors independently assessed the risk of bias in each study, based on the guide to the Cochrane Manual for Systematic Intervention Reviews (Spanish version) [20]. Top: assessments by P-RMA; bottom: assessments by S-RJA

[19]. Independently, two researchers (P-RMA and S-RJA) assessed the risk of bias for each study, based on the guide to the Cochrane Manual for Systematic Intervention Reviews in its Spanish version [20]. Each study was given a bias risk rating ("low risk", "uncertain risk", or "high risk") for the following criteria: random sequence generation, concealment in the assignment; blinding participants and researchers; incomplete results report; and selective results report. Figure 1 summarizes the analysis by each of the independent assessments for each included study.

Statistical analysis

A meta-analysis was conducted following the recommendations provided in the Cochrane Manual of Systematic Intervention Reviews [20], using the Review Manager software (RevMan, v. 5.3). The methods, results, and population heterogeneity were evaluated to determine the subsequent meta-analysis suitability. Because the variables were quantitative, continuous data were used to calculate the difference between means (with 95% confidence intervals), and because different variables or identical variables with different scales were compared, the standardized mean difference (SMD) was chosen as the measure of effect size (which was estimated by Hedge's *g* by the inverse variance

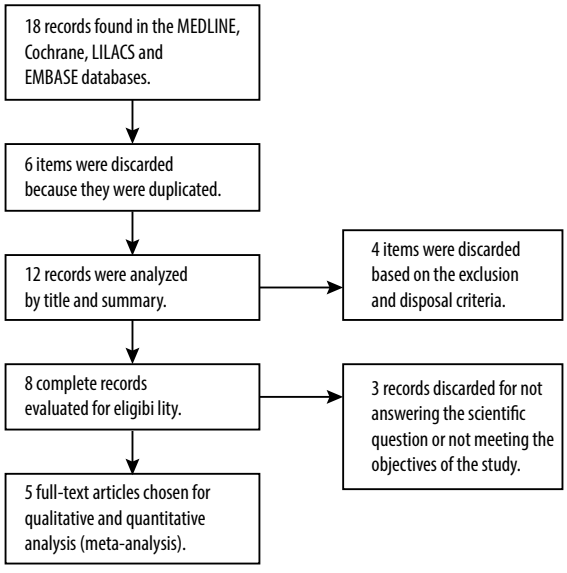


Figure 2. Systematic review flowchart

method in a fixed-effects model). The analysis was performed by P-RMA and supervised by S-RJA.

Results

Searching electronic data sources resulted in a total of 18 articles, of which 6 were eliminated because they were duplicates. Of the 12 remain articles, their title and summary were analyzed based on the selection criteria, and 8 articles were identified for having their content thoroughly analyzed to define their relevance in this systematic review. At the end of this phase, 3 were eliminated for not meeting the inclusion criteria, and 5 articles were included. The search strategy is summarized in Figure 2.

Of the 5 articles included, 2 were randomized, and 3 were non-randomized clinical trials. A total of 187 participants were included. There were 135 individuals who met the diagnostic criteria for ADD with and without hyperactivity. Individuals who started MPH treatment at the beginning of the study were included, such as those with prolonged prescription (more than 4 years). In all cases, the dose was less than 20 mg per day (<0.6 mg/kg/day). Of these individuals, 44 were diagnosed with CAPD based on clinical and audiological criteria; the remaining 52 individuals were used as a reference, with no evidence of these disorders. The randomized trials had a crossover design, and made comparison to a placebo; the same patients (with ADD) were experimental subjects and controls. Another non-randomized trial followed the same strategy, albeit without MPH as control. The remaining studies used initial evaluation and re-evaluations (after 3, 6, or 9 months of treatment) as the control strategy. All authors of the included studies reported no conflicts of interest. Two non-randomized trials did not reveal the source of their funding.

MPH effect on selective auditory attention and auditory integration or closure

This was evaluated by the speech-in-noise test performed on 167 participants (115 with diagnosis of ADD, 44 with ADD and CAPD, and 52 reference controls) in four clinical trials, two randomized [10, 18] and two non-randomized [15, 21]. The MPH effect resulted in an SN test performance increase (0.38 SMD [95% CI 0.11 to 0.66]) with respect to the evaluation of the control group (without treatment or placebo) ($Z = 2.7$, $p = 0.007$]). This effect was consistent both in acute effect (10 h without treatment) and in chronic use (3 months treatment). The inconsistency effect was of low importance ($I^2 = 18\%$, $p = 0.3$) (Figure 3).

MPH effect on selective audition, rapid decoding, binaural integration, or sequencing

This effect was evaluated by staggered spondaic words tests on 99 participants (67 with ADD, 32 with ADD and TPAC, and 29 reference controls) in two clinical trials: one randomized [10] and the other non-randomized [21]. Since the clinical trial of Cavadas et al. (2007) [21] showed the result as the average proportion of the yield obtained relative to the mean of the reference controls, while that of Tillery et al. (2000) [10] as the mean of total errors obtained, the latter parameter had to be normalized (multiplied by –1) for both effects to follow the same direction. The MPH effect resulted in an SSW test performance increase (0.35 SMD [95% CI 0 to 0.69]) with respect to the evaluation of the control group (without treatment or placebo) ($Z = 1.95$, $p = 0.05$). This effect was consistent both in acute effect (10 h without medicine) or chronic use (3 to 9 months of treatment). The inconsistency effect was of low importance ($I^2 = 27\%$, $p = 0.24$) (Figure 4).

MPH effect on attention maintenance, concentration, and auditory impulsivity

This was evaluated by continuous performance tests on 52 participants, all diagnosed with ADD and CAPD, in two clinical trials, one randomized [10] and the other non-randomized [11]. The MPH effect resulted in a decrease in the number of errors and anticipated responses of the test of –0.77 SMD (95% CI –1.17 to –0.37) concerning the evaluation of the control group (without treatment or placebo) ($Z = 3.79$, $p = 0.0002$). Both studies determined the acute effect of the drug. The effect inconsistency was null ($I^2 = 0\%$, $p = 0.78$) (Figure 5).

MPH effect on discrimination, memory, auditory sequencing ability, and combination of phonemes

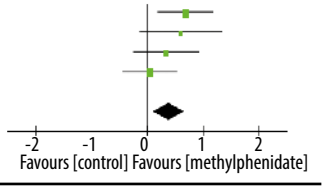
This effect was evaluated by the filtered word, frequency pattern, and phonemic synthesis tests on 100 participants (77 with ADHD, 44 with ADHD and CAPD, and 23 reference controls) in three clinical trials: two randomized [10, 18] and one non-randomized [15]. The effect of MPH was an increase in test performance of 0.35 SMD (95% CI from 0.01 to 0.68) with respect to the control group (without treatment or placebo) ($Z = 2.03$, $p = 0.04$). This effect was consistent both in acute effect (10 h without medicine) and in chronic use (3 months of treatment). Also, the effect inconsistency was null ($I^2 = 0\%$, $p = 0.48$) (Figure 6).

Discussion

This systematic literature review provides a critical analysis of the studies regarding the possible beneficial effect

Figure 3. MPH effect on selective auditory attention and auditory integration or closure

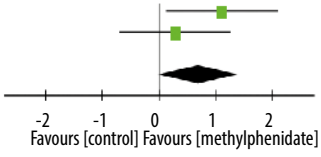
	Methylphenidate			Control				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
Cavadas 2007	82.2	7.61	29	75.11	11.94	38	31.3%	0.68 [0.18, 1.18]	
Cook 1993	88.78	10.45	14	81.4	13.2	15	13.9%	0.60 [–0.15, 1.35]	
Lanzetta-Valdo 2017	19.75	2	18	19	2.3	30	22.4%	0.34 [–0.25, 0.92]	
Tillery 2000	28.35	9.58	32	28	9.58	32	32.3%	0.04 [–0.45, 0.53]	
Total (95% CI)			**93**			**115**	**100%**	**0.38 [0.11, 0.66]**	



Heterogeneity: $Chi^2 = 3.65$, df = 3 ($p = 0.30$); $I^2 = 18\%$ Test for overall effect: Z = 2.70 ($p = 0.007$)

Figure 4. MPH effect on selective auditory, rapid decoding, binaural integration, or sequencing, or any combination of these

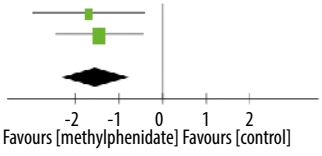
	Methylphenidate			Control				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
Cavadas 2007	91.42	8.79	29	85.77	10.92	38	49.8%	0.56 [0.06, 1.05]	
Tillery 2000	–16.47	11.04	32	–18.1	11.95	32	50.2%	0.14 [–0.35, 0.63]	
Total (95% CI)			**61**			**70**	**100%**	**0.35 [0.00, 0.69]**	



Heterogeneity: $Chi^2 = 1.37$, df = 1 ($p = 0.24$); $I^2 = 27\%$ Test for overall effect: Z = 1.95 ($p = 0.05$)

Figure 5. Effect of MPH on maintaining attention, concentration, and auditory impulsivity

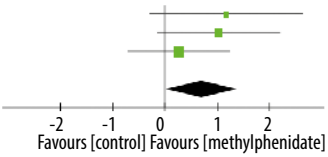
	Methylphenidate			Control				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
Keith 1999	0.48	0.63	20	1.27	1.13	20	37.8%	–0.85 [-1.5, -0.20]	
Tillery 2000	15.14	10.31	32	25.8	17.69	32	62.2%	–0.73 [-1.23, -0.22]	
Total (95% CI)			**52**			**52**	**100%**	**–0.77 [–1.17, –0.37]**	



Heterogeneity: $Chi^2 = 0.08$, df = 1 ($p = 0.78$); $I^2 = 0\%$ Test for overall effect: Z = 3.79 ($p = 0.0002$)

Figure 6. MPH effect on discrimination, memory, auditory sequencing ability, and combination of phonemes

	Methylphenidate			Control				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
Cook 1993	90.67	10.33	15	77.33	29.63	15	21.0%	0.58 [–0.15, 1.32]	
Lanzetta-Valdo 2017	22.3	6.7	18	18.9	6.4	30	32.0%	0.51 [–0.08, 1.11]	
Tillery 2000	18.5	4.25	3	17.9	4.8	32	47%	0.13 [–0.36, 0.62]	
Total (95% CI)			**65**			**77**	**100%**	**0.35 [0.01, 0.68]**	



Heterogeneity: $Chi^2 = 1.45$, df = 2 ($p = 0.48$); $I^2 = 0\%$ Test for overall effect: Z = 2.03 ($p = 0.04$)

on CAPD in children and adolescents with ADD who were treated with MPH. Evidence showed a positive MPH effect compared with respective controls (without MPH or placebo) with low or null inconsistency (heterogeneity). The risk of inaccuracy could not be determined because selected clinical trials did not assess complications or side effects. The MPH doses used in this intervention were the usual (0.2 to 0.6 mg/kg/day), and we assumed that the demonstrated effect did not go along with an increase in adverse effects [22].

Central auditory processes are responsible for sound localization and lateralization; auditory discrimination; auditory pattern recognition; temporal aspects of audition, including temporal resolution, temporal masking, temporal integration, and temporal ordering; and proper auditory performance in the presence of competing and degraded acoustic signals. The ability to divide attention between different auditory stimuli and abstract information from incomplete sources to make sense of them is a key skill of the CAP [15]. Three of the four clinical trials showed that ADD patients performed worse on the speech-in-noise test compared to controls (without age or sex adjustments) [15,18,21].

A considerable intervention size effect was found with MPH: approximately a 5% improvement on a 1 to 100 scale [21]. However, three studies [10,15,18] showed variability below the effect threshold in favor of MPH. This inconsistency in the individual evaluation of the trials could be explained by the origin of the individuals: two Brazilian trials [15,21] and two American trails [10,18] were included. It is, therefore, necessary to determine the effect of language on the reproducibility of the results. Although the evidence indicated that MPH improved selective auditory attention and auditory integration or closure, the applicability in Spanish-speaking populations is limited, given the differences in these tests in Lusophone and English-speaking populations [23].

Limitations

Figure 1 summarizes the potential biases of the analyzed studies. Two clinical trials [15, 21] were controlled, but not randomized, so these are considered as having a high risk of selection bias. Also, it is not possible to differentiate the MPH effect on CAP, outside the context of ADD. This is because this drug is not indicated for CAPD [11]. All CAP tests analyzed are only available in a few languages, and many of them lack validation as part of CAPD [24]. CAPD remains an evolving concept, so its diagnosis is complex and heterogeneous, even in the most specialized centers [2].

Conclusion

MPH has a discrete but favorable effect on CAPD, including: in auditory selective attention and auditory integration or closure; selective auditory, rapid decoding, and binaural integration or sequencing; in the maintenance of attention, concentration, and auditory impulsivity; and on discrimination, memory, auditory sequencing abilities, and phoneme combination among individuals with ADD under MPH treatment.

Perspectives and recommendations

Studies evaluating the direct effects of MPH on CAP are now needed, regardless of the ADD and on the consequences of the lack of management, on learning, socialization, quality of life, or integration of these individuals. It therefore seems desirable to conduct randomized studies on groups of children with CAPD without features of ADHD. It is also important to review the potential acute and chronic side effects of MPH in these individuals.

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